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PERSPECTIVE
A Rheostat Model for a Rapid and Reversible Form of Imprinting-Dependent Evolution

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The evolutionary advantages of genomic imprinting are puzzling. We propose that genomic imprinting evolved as a mechanism that maximizes the interindividual variability in the rates of gene expression for dosage-sensitive loci that, with minimal unrelated deleterious effects, can alter the phenotype over a wide continuum. We hypothesize (1) that genomic imprinting provides a previously suggested haploid selective advantage (HSA); (2) that many imprinted genes have evolved mechanisms that facilitate quantitative hypervariability (QH) of gene expression; (3) that the combination of HSA and QH makes possible a rapid and reversible form of imprinting-dependent evolution (IDE) that can mediate changes in phenotype; and (4) that this enhanced adaptability to a changing environment provides selective advantage to the population, as an assisted form of evolution. These mechanisms may have provided at least one of the driving forces for the evolution of genomic imprinting in mammals. The rheostat model suggests that both genetic and epigenetic variants can contribute to an integrated mechanism of mixed Mendelian and non-Mendelian inheritance and suggests the possibility that the majority of variants are not intrinsically deleterious but, depending on the environment, are each potentially advantageous. Moreover, this would be a reversible form of evolution, with the ability not only to protect a silent allele from selection for many generations but to reactivate and expand it in the population quickly.

Introduction

Genomic imprinting is generally defined as an epigenetic phenomenon in which the expression of a gene or chromosomal region is reversibly modified, depending on the sex of the transmitting parent, but in which the modification does not include a change in DNA sequence. In the case of single genes, this often equates to the partial or complete silencing—on the basis of parental origin—of one of two alleles for a diploid locus. Although some authors (Lloyd et al. 1999; Lloyd 2000) have defined genomic imprinting broadly to include phenomena in insects and fish, imprinting is more often described narrowly, to include imprinted expression of naturally occurring genes. By this definition, imprinting is relatively widespread in plants and mammals but is rare or absent in egg-laying vertebrates.

Genomic Imprinting in Mammals

A recent and excellent review of genomic imprinting in mammals is available, including a detailed bibliography (Reik and Walter 2001). Imprinted genes in mammals are generally found in clusters referred to as "imprinted domains," and, as often as not, oppositely imprinted genes occur within a single domain. In brief, in mammalian genomic imprinting, one or the other parental allele is systematically silenced in normal embryos and/or adults, often in a tissue-specific manner, and the silencing is often leaky. Currently, there are >50 known imprinted genes identified in mice and/or humans (see the Mammalian Genetics Unit, Harwell UK Web site). In the mouse, many chromosomal regions associated with imprinting show phenotypic effects on growth, viability, or behavior, or some combination of the three. In addition, the phenotypic effects of individual genes often involve growth or behavior, but the phenotypic effects of many imprinted genes are not known.

The paternal and maternal chromosomes of most imprinted domains display differentially methylated regions (DMRs) of DNA, as well as differential gene expression. These non–sequence-based differences, in DNA methylation, chromatin structure, and gene expression, between the paternal and maternal chromosomes are referred to collectively as the paternal or maternal "epigenotype." Regions enriched for CpG dinucleotides (i.e., CpG islands) are frequent in imprinted domains and are often differentially methlyated, according to parent of origin. In contrast, CpG islands found in nonimprinted regions are usually unmethylated (Bird 2002). Antisense and non-

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coding RNA transcripts are also frequent within imprinted domains, and chromatin boundary elements, or "insulators," occur within imprinted domains (Bell and Felsenfeld 2000; Hark et al. 2000; Wolffe 2000; Sleutels et al. 2002). Some features may be unique to imprinted domains, and others may be present with increased frequency.

An imprinting center can often be identified within an imprinted domain, as a genomic region that alters the epigenotype of the chromosome, in *cis,* when it is mutated or deleted. The "gametic mark" refers to the ability of a region to set the epigenotype. Gametic marks and imprinting centers overlap conceptually and often are found within or near a differentially methylated CpG island. Two forms of silencers can be distinguished in imprinted domains. One type is methylated on the repressed allele and is unmethylated on the expressed allele, whereas the other is methylated on the expressed allele and is unmethylated on the repressed allele. Thus, there are examples of oppositely methylated DMRs within a single gene. Mechanisms exist to erase, set, and maintain the proper epigenetic state of the paternal and maternal chromosomes for an imprinted domain. There are major waves of demethylation and methylation that occur during mammalian development, and a gametic mark typically is protected from the major wave of demethylation that occurs before the blastocyst stage; for details, see the discussions of Reik et al. (2001). Epigenetic modifications within imprinted domains include differential methylation of DNA, differential acetylation of histones (Grunstein 1997; Jenuwein and Allis 2001), and differential methylation of histones (Nielsen et al. 2001; Xin et al. 2001).

What Biological Advantage Has Promoted the Evolution of Genomic Imprinting?

The potential evolutionary advantages and disadvantages of genomic imprinting are complex. Although the benefits and hazards of haploidy versus diploidy have been debated and defined to a significant extent (Kondrashov and Crow 1991), genomic imprinting blends the two states such that individuals may be functionally haploid but the population explores the advantages of virtually all alleles in the diploid genome over two or a few generations. Any disadvantage of functional haploidy must be outweighed by some advantage conferred by genomic imprinting. It is important to consider whether any advantage or increased fitness is at the level of the individual or the group (species or deme). We are proposing a model whereby individuals would be directly subject to selection but the benefit would accrue only to the group through greater phenotypic variability. Gould and Lloyd (1999, p. 11904) have suggested that "two major clarifications have greatly abetted the understanding and fruitful expansion of the theory of natural selection in recent years: the acknowledgment that interactors, not replicators, constitute the causal unit of selection; and the recognition that interactors are Darwinian individuals, and that such individuals exist with potency at several levels of organization (genes, organisms, demes, and species in particular), thus engendering a rich hierarchical theory of selection in contrast with Darwin's own emphasis on the organismic level." We are proposing that increased quantitative variability for certain genes will confer selective advantage on the group. It can be debated whether this is an example of "soft group selection" or "hard group selection," the latter of which has been defined by Mayr (1997, p. 2092) as meaning that "owing to a division of labor or other social actions, the fitness of the group is higher or lower than the arithmetic mean of the fitness values of the composing individuals." This increased adaptability to a changing environment would provide selective advantage to a deme or species, a feature that might be particularly relevant to the evolution of human behavior. It is even possible that, during evolution, a substantial fraction of all genes will have been exposed to the triggering events that could initiate imprinting but that imprinting has provided selective advantage for only a subset of loci.

Hurst (1997) has distinguished and critiqued a long list of theories as to why genomic imprinting has evolved in diverse species, focusing on mammals, and Bartolomei and Tilghman (1997) also have evaluated various hypotheses. The theories include arguments that imprinting exists to (1) prevent parthenogenesis, (2) inhibit the invasiveness of the placenta, (3) regulate loss or gain of chromosomes, (4) alter the dominant and recessive relationships of alleles, (5) minimize variation in rates of expression, or (6) provide other biological advantages. Despite the many theories, the biological significance of genomic imprinting remains puzzling.

The Genetic-Conflict Model

Of the numerous models and theories proposed to "explain" the evolution of genomic imprinting, the genetic-conflict model currently is considered to be the most cogent. This hypothesis was first described as a "parental tug-of-war" (Moore and Haig 1991) and was based on the premise that paternal evolutionary interests were served by increased fetal growth and that those of the mother were served by smaller fetal size. It was suggested "that imprinting has evolved in mammals because of the conflicting interests of maternal and paternal genes in relation to the transfer of nutrients from the mother to her offspring" (Moore and Haig 1991, p. 45). A number of the initial, growth-related genes identified, such as murine insulin-like growth factor-2 (*Igf2*) and a related receptor (*Igf2r*), are expressed in a manner that would fit this model. We are proposing a genomic-im-

printing model that we believe is attractive either alone or in combination with the conflict model.

Haploid Selective Advantage (HSA)

Although a detailed review of evolutionary theories of genomic imprinting does not separate HSA as a distinct theory (Hurst 1997), it is implicit in many of the hypotheses, and it has been well appreciated that allelic silencing implies some benefit derived from haploid expression of imprinted genes (Hurst 1998). The most explicit statements on the potential advantages of haploid expression come from McGowan and Martin (1997, p. 499), who speculate "that imprinting may actually be a simple genetic mechanism to enhance the efficient evolution of both individual genetic loci and combinations of loci with related functions, without risking the population as a whole." McGowan and Martin (1997) go on to make several important points: (1) the relevance of functional hemizygosity (haploidy) to natural selection; (2) the effective removal of alleles from selection when silenced, even, to some extent, if silencing is leaky; (3) the freedom of silent alleles to mutate; (4) the potential for increased mutation of silenced alleles secondary to methylation of cytosine; (5) the existence of four historically different alleles for imprinted genes in the F2 generation; (6) the ability of alleles to move back and forth between an unselectable pool of alleles and a selectable pool of alleles; (7) the potential of all loci to become imprinted in the history of a species; (8) the consideration of imprinted genes as being subject to enhanced evolution; (9) the potential for imprinting to facilitate coevolution of genes that are functionally related but unlinked; (10) the potential for prolonged residence in an unselectable pool, to allow for greater modification of an allele; and (11) the potential to increase the variability and efficiency of evolution of an imprinted gene. McGowan and Martin (1997) also recognize the previous suggestion by Varmuza (1993)—that the status of a locus could switch repeatedly between imprinted and nonimprinted. Varmuza (1993) also emphasized the potential for this variation of imprinted status to contribute to speciation. We wish to embrace the concept of HSA as an integral part of the driving force for the evolution of genomic imprinting in mammals; furthermore, we propose that this is particularly relevant to the selection of quantitative variants in the level of expression that correlate with a phenotypic continuum that provides valuable diversity and adaptability with minimal deleterious effects.

Quantitative Hypervariability (QH) for Imprinted Genes

Geneticists and evolutionary biologists are acclimated to the concept that the coding properties of some genes, such as those for histones, are highly conserved both between species and between individuals within a species, whereas others, such as those for histocompatibility antigens, are highly variable between species and between individuals within a species. It is not customary to focus similarly on the possibility that some genes, such as those for histones, might be relatively constant for abundance of expression as measured in protein molecules per specified cell type, whereas others, perhaps those for growth factors, might be highly variable for the level of expression. This variability could occur between species, between individuals within a species, and, unlike most coding variation, between different tissues within the same individual.

We propose that many, perhaps most, imprinted genes are controlled in a manner that is similar to the way in which a rheostat uses a variable resistance to adjust the current in an electrical circuit (e.g., a light dimmer). This implies that a gene acquires a new dimension in its regulation, allowing substantial, rapid, and reversible changes in the level of gene expression. Our discussion will focus on genetic and epigenetic effects that are transmitted through the germline as contrasted, to somatic variation, which can be considered as a separate topic. We hypothesize that imprinted loci might be quantitatively hypervariable, both for their level of gene expression and for the resultant phenotypic trait; this would provide substantial and reversible variation along a continuum. We also propose that these QH imprinted genes are the evolutionarily relevant targets of the haploid selection; these genes often affect growth and/or behavior—and, perhaps, other traits. We use the term "QH genes" (1) to distinguish these genes from any that might be only incidentally imprinted through hitchhiker effects, (2) to imply that maximizing the quantitative rather than qualitative variation in expression for these genes may be particularly relevant to their selective advantage, and (3) to reserve the possibility that there might be classes of imprinted genes that do not fit the QH model.

Rheostat Model: HSA and QH Loci Combine for Imprinting-Dependent Evolution (IDE)

Our major proposal is that HSA acting on quantitatively hypervariable loci makes possible a rapid and reversible form of IDE. We propose to designate this hypothesis as a "rheostat model" for genomic imprinting (fig. 1*A*). The rapid and reversible properties are envisioned as a specialized or assisted form of evolution that provides selective advantage for a subset of loci when variation back and forth over a phenotypic continuum can provide advantageous adjustment to a changing environment.

There are numerous perspectives to the rheostat model. These include the potential for both genetic and epigenetic variation; the possibility that, for these loci, epigenetic

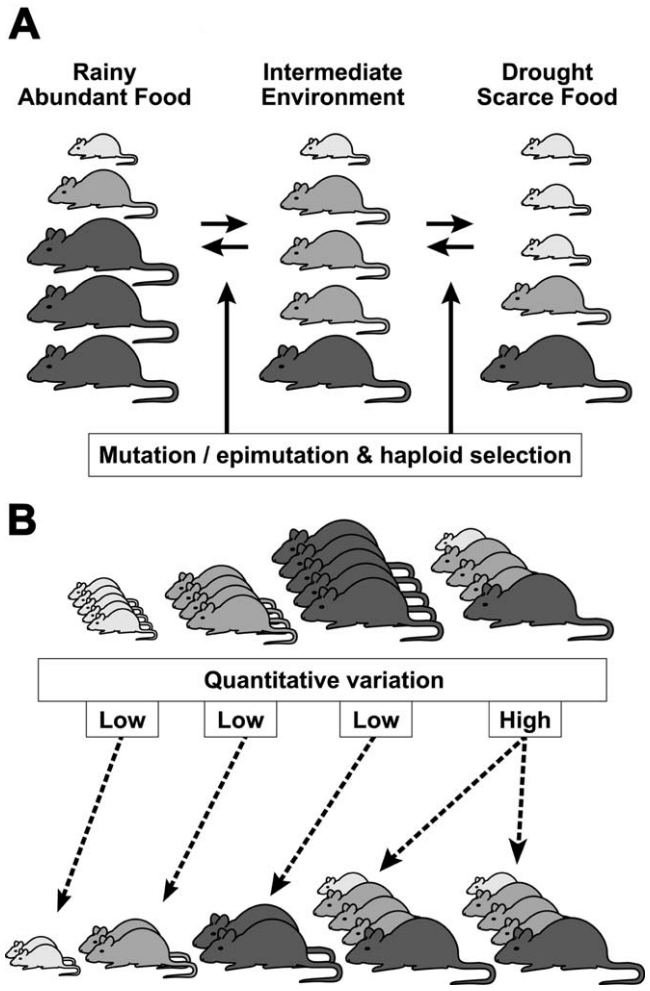

Figure 1 Rheostat model. *A*, Depiction of how the rheostat model might function to allow variation in body size in response to the environment through mutation and epimutation followed by HSA. *B*, Depiction of how selective advantage might accrue over multiple generations and environmental cycles to a group that is more variable for body size (right) compared to three groups of different but less variable sizes.

germline variation is considerably more frequent than genetic germline variation; the potential for direct and rapid selection of alleles, through interaction between a functionally haploid genotype and the environment; the ability to protect an allele from selection for availability at a future date; the advantages of reversibility; the ability to have a large proportion of variants be potentially useful (i.e., not intrinsically disadvantageous); the effect of leaky silencing; and the potential value of being polymorphic for imprinting. As depicted in figure 1*B*, although individuals would be subject to selection, the selective advantage would accrue primarily to the group, not to the individual, thus giving the group increased variability and adaptability for certain traits, such as body size.

Epigenetic variation—including DNA methylation, histone acetylation, and histone methylation—is common within imprinted domains (Wolffe and Matzke 1999; Bird 2001), and this provides the potential for epigenetic variants to contribute to hypervariability in the level of expression, without varying the coding sequence. Epigenetic germline variation would generate "epialleles" (i.e., variants in DNA methylation or chromatin structure that are potentially transmissible across the germline but that do not differ in nucleotide sequence) that are likely to be semiheritable in a non-Mendelian fashion; these epialleles might be well suited for reversibility.

We propose that imprinted and differentially methylated CpG islands will be associated with greater genetic and epigenetic variation than are the majority of CpG islands, which are unmethylated, and we propose that this increased variation will be expressed as variability in the abundance of the gene product associated with the CpG island. There is surprisingly little information about the inheritance and variability of DNA methylation, although there is evidence that patterns are tissue specific and transmitted through the germline (Silva and White 1988). Although it is recognized that CpG dinucleotides show a higher frequency of polymorphism (Barker et al. 1984) and are hotspots for disease-causing mutations (Sommer et al. 2001), these represent changes in DNA sequence, rather than changes in epigenotype. We are not aware of systematic studies, of either polymorphism or inheritance of DNA methylation in human families, that have sought to obtain any insight into "epimutation rates." Bisulfite sequencing could be used in the study of families, to determine rates of epimutation, but the ability of DNA methylation to vary by age and tissue type would need to be taken into account. It is known that there are extensive DNA-methylation differences between mouse strains (Shibata et al. 1995), and there is some evidence for transgenerational transfer of patterns DNA methylation (Morgan et al. 1999; Reik and Dean 2001).

Under the rheostat model, as quantitative variants arise, functional haploidy could allow for both direct selection and much-more-rapid enrichment of new genotypes and phenotypes in the population than would be possible with diploid expression. Traditionally, the ability of organisms to make relatively rapid evolutionary adaptations to the environment is attributed to the presence of allelic heterogeneity in the population. Under the rheostat model, genomic imprinting can complement, but not replace, this heterogeneity and thereby enhance the potential for rapid adaptation to the environment. Through silencing, imprinting allows an allele that is temporarily less advantageous to be completely pro-

tected from selection indefinitely, by serial passage in the sex that silences the allele; the allele remains available for a future date, when a change in the environment makes it more advantageous.

Reversibility of evolutionary adaptation could be an advantageous feature of IDE. A species is likely to encounter cyclical changes in the environment, such as intervals of drought and abundant rainfall. Similarly, there are likely to be periodic and recurring variations in the abundance of food, the prevalence of specific predators, and other environmental components. Through hypervariability, IDE can provide reversibility of phenotype, such as the ability to vary back and forth between smaller and larger body size, whereas genetic variation might be less effective. Epigenetic germline variation could be an important, non-Mendelian component of phenotypic reversibility.

Evolutionary theory generally assumes that the great majority of mutations will be deleterious, but, under the rheostat model, this need not be the case for imprinted loci. If there is epigenetic and genetic hypervariability of the level of expression, and if this variation confers a continuum of phenotype that may be of varying suitability for a given environment, then the majority of variants can be conditionally advantageous—that is, each variant may be advantageous, depending on the changing environment.

Under the rheostat model, both the presence or absence of imprinting and the tightness of silencing could be quite variable; that is to say, genomic imprinting might be predicted to be polymorphic both within and between species. We envision an imprinted gene to have acquired a new regulatory dimension and consider it to be intrinsically more flexible—and, therefore, more biologically advantageous—than its nonimprinted counterpart. While acquiring this new flexibility, an imprinted gene maintains the possibility of switching back and forth between imprinted and nonimprinted status.

What Kind of Genes "Attract" Genomic Imprinting?

We hypothesize that a subset of dosage-sensitive genes—that is, those that generate a phenotypic continuum, without unrelated deleterious effects—are eminently suitable to benefit from genomic imprinting. This subset would not include dosage-sensitive genes for which varying the level of expression leads to an impaired phenotype, as in the case of the *PMP22* gene and Charcot-Marie-Tooth disease (Boerkoel et al. 1999); nor would it include the many transcription factors for which haploinsufficiency leads to malformations (Seidman and Seidman 2002). The potential relevance to gene dosage has been pointed out by Hurst and McVean (1998, p. 706), and we agree with their speculation that "perhaps some dose-sensitive genes attract the imprint machinery." The phenotypic continua that we envision would represent a spectrum of phenotypes such that different variants might be most advantageous, depending on the environment. Genes that affect growth or behavior are two groups that, through suitability for selection over a continuum, might "attract" imprinting, and other classes of imprinted phenotypic traits might be discovered. Thus, it might be more advantageous to be large or small or to be hyperactive or hypoactive, depending on food supply, predators, or level of rainfall. This reasoning implies that imprinted genes, acting singly or in combination, might function as quantitative-trait loci (QTLs) determining the phenotype along a continuum. By this rationale, genes that are not dosage sensitive are not likely to evolve to be imprinted.

How Might the Properties of Imprinted Domains Contribute to QH?

QH implies that there is a mean amount of variability for the level of expression of genes, in terms of protein molecules per specified cell type, and that, for this parameter, some genes would be substantially more variable than others, both between species and between individuals or strains within the same species. We suggest that differential DNA methylation of promoters, *cis*-acting imprinting-control elements, boundary elements, enhancers, and silencers could contribute to QH. We propose that other properties that are associated with imprinted genes—such as noncoding RNAs, boundary elements, competition for *cis*-acting elements, direct repeats containing alternative exons, antisense transcripts, and histone modification—also might contribute to quantitative variability of expression of imprinted genes, compared with nonimprinted genes. Although most or all of these regulatory features found in imprinted domains might occur for nonimprinted genes, we hypothesize that imprinted genes are *enriched* for these properties. Changes in DNA methylation, histone modification, and other aspects of chromatin structure that occur between one generation and the next may be a particularly prominent source of the hypervariability. The proposed variability for the level of expression might be largely transcriptional, but posttranscriptional regulation could play a role, as in the case of upstream open reading frames in bicistronic imprinted transcripts (Gray et al. 1999), alternative 5′-UTR sequences, and, perhaps, antisense transcripts. There are multiple ways in which antisense or noncoding RNA transcription might reduce the abundance of the sense transcript in *cis* or in *trans*. These could include transcriptional gene silencing, posttranscriptional gene silencing, and RNA interference, the latter two of which are potentially quite similar (Wolffe and Matzke 1999; Hammond et al. 2001; Matzke et al. 2001; Sleutels et al. 2002).

Table 1

Fit of the Rheostat Model of Genomic Imprinting to Existing Data

Observations[a]	Interpretation
Comparative data, evolved independently in plants and mammals	Arise easily through transient advantage to allelic silencing in changing environment
Growth effects	Growth-related genes "attract" imprinting, on the basis of suitability for selective advantage through hypervariability over a continuum
Behavior effects	Like growth, behavioral traits are suitable for selection over a continuum of phenotype
Multiple genes imprinted	Any locus is susceptible
Maternal or paternal silencing	HSA independent of parental allele; possible biases
Not every chromosome has an imprint	Not necessary by hypothesis
Strange effects on lethality	Imprinting machinery rapidly evolving
Change of status between species	Imprinting machinery rapidly evolving
Tissue specificity	Potential for tissue-specific haploid selection
Coding regions of imprinted genes not rapidly evolving	Coding regions are subject to usual selective pressure to conserve function
Fewer and smaller introns	Regulatory and nonessential regions are rapidly evolving
Asynchronous replication	Secondary to changes in chromatin structure
Chromosomal clustering	Imprinting machinery prone to spreading effects

[a] Modified from Hurst (1997).

Determination of Which Parental Allele Is to Be Silenced

Under the rheostat model, the determination of which parental allele is silenced could be affected by a number of factors. The model can provide most or all of the proposed evolutionary advantages, without regard to which parental allele is silenced. The determination of which allele is silenced might occur independently for each domain or locus and might be entirely stochastic, with equal likelihood that either parental allele would be silenced, as presumably is the case for immune-related allelic exclusion. The completely stochastic possibility seems relatively unlikely under the rheostat hypothesis, particularly because the mechanisms for silencing might be likely to introduce a bias, as occurs in the case of imprinted transgenes (Chaillet 1994). The genetic-conflict model can fit nicely with the rheostat model, with the conflict determining which allele will be silenced and potentially contributing to the evolutionary benefit of imprinting. The genetic-conflict model might be especially influential in determining which parental allele will be fixed as silenced for growth-related genes, and it might or might not apply to other imprinted genes or phenotypes. Another factor that might determine which parental allele is silenced for growth-related genes is the size of mother relative to the size of offspring, as it relates to the birth process and the nutrition of the offspring. These effects could be complex and somewhat distinct from those included in the genetic-conflict model, but these questions will not be discussed in detail here.

Fit of the Rheostat Hypothesis to Existing Data

There are extensive existing data that bear on evolutionary theories of genomic imprinting, and Hurst (1997, p. 212) has suggested some "facts that should be explained" by any hypothesis or model. We have addressed a slightly modified version of his criteria, in table 1. Interspecies comparisons suggest that genomic imprinting has evolved independently in widely divergent species such as plants and mammals, but imprinted genes are yet to be identified in egg-laying vertebrates. We believe that the rheostat hypothesis is quite satisfying in regard to the apparent multiple independent origins of imprinting, because the model can readily explain the origin of imprinting. Consider growth, as well as the possibility that, in response to the environment, a mammal may have evolved to be a relatively large size. If food were to become scarce, then there might be benefit to silencing of one of two growth-promoting alleles, if it were assumed that smaller body size would be advantageous in the then-current environment. Inheritance of the silenced allele would be advantageous, and imprinting could quickly become established. Table 1 attempts to explain the way in which many of the other features of imprinted expression might fit within the rheostat model.

Potential for Non-Mendelian or Transgenerational Effects

The inheritance of differences in DNA methylation is potentially non-Mendelian. In mice, there is evidence that differences in DNA methylation can persist over multiple generations and can change in gradations. In studies of a modified allele of the agouti locus, Whitelaw and colleagues (Morgan et al. 1999; Rakyan et al. 2001) have presented evidence for incomplete erasure of an epigenetic modification in the germline, resulting in "epigenetic inheritance." They concluded that "the distribution of phenotypes among offspring is related to the phenotype of

the dam" (Morgan et al. 1999, p. 314). Even more stunning, in terms of non-Mendelian behavior, is the ability of a β-galactosidase–expressing transgene to be transmitted in a methylated and silent state, for as many as three generations and irrespective of the sex of transmission, and subsequently, by breeding to a different mouse strain, to be reactivated in an all-or-none manner (Sutherland et al. 2000). A report that dietary folate and methyl-donor compounds can alter DNA methylation and gene expression across generations in mice raises the possibility of semiheritable, environmental effects on gene expression (Wolff et al. 1998). Thus, it becomes clear that genomic alterations other than DNA sequence changes (e.g., changes in DNA methylation, histone modification, and chromatin structure) can occur in response to endogenous, stochastic, and environmental factors and can be transmitted in a semiheritable way that would be definitively non-Mendelian.

Pembrey (1996) has reviewed some of the ways in which imprinting might lead to what he has described as "transgenerational" effects. This can occur if some endogenous or environmental effect can lead to alteration of DNA methylation in germ cells. Since the methylation pattern can be transmitted across mitosis and, to a more limited extent, across meiosis, a change in gene expression may be acquired and transmitted across generations (Morgan et al. 1999; Balter 2000). Pembrey (1996) has suggested that (*a*) the reduced birth weight of infants whose grandmothers suffered acute starvation during pregnancy and (*b*) the secular increase in childhood growth during the past century might be examples of such imprinting-related transgenerational effects.

Testing the Rheostat Model

In our view, the rheostat model makes a number of predictions and raises some interesting questions. It would be desirable to examine rates of change in DNA methylation across generations. Are imprinted genes indeed more variable in their level of gene expression than are nonimprinted genes? Are antisense and noncoding RNAs truly more frequent in imprinted than in nonimprinted domains? Do features such as antisense and noncoding RNAs function primarily to vary the rate of expression for an associated coding gene? Do the regulatory and nonessential regions of imprinted genes evolve more rapidly than those of nonimprinted genes? Is the molecular basis of miniature strains of mammals (proportionate variants, not skeletal dysplasias) explained primarily by changes in expression of imprinted genes, and is the phenotype of body size in mammals prominently affected by epigenetic as well as genetic inheritance? Is genomic imprinting more polymorphic between individuals and between species than is currently documented, and is it a major determinant of speciation? In addition to these experimental questions, it will be important to develop mathematical evaluations of the rheostat model.

Assisted Evolution

Under the rheostat model, we propose that genomic imprinting makes possible a rapid and reversible form of evolution. There is some precedent for the possibility that organisms might evolve mechanisms to speed or alter evolution, a type of facilitated evolution (Chicurel 2001*a*, 2001*b*). For example, Dover (2000, p. 17) has argued that many biological phenomena—including "the total phenomenology of differential promoter utilization, DNA modification, differential DNA and RNA splicing, RNA editing, and post-translational modification"—might be envisioned as facilitating evolution. Many epigenetic phenomena in plants and fungi might be envisioned as having evolved to enhance adaptability to the environment; for a review, see the work of Henikoff and Matzke (1997).

Lindquist and colleagues have suggested a capacitor model for morphological evolution; in this model, conformational changes in proteins, as influenced by the heat-shock protein Hsp90 (Rutherford and Lindquist 1998), and changes in a yeast prion (Lindquist 2000; True and Lindquist 2000) can provide "an explicit molecular mechanism that assists the process of evolutionary change in response to the environment" (Rutherford and Lindquist 1998, p. 341). Under the capacitor model, altered function of Hsp90 in *Drosophila* uncovers a multitude of developmental variants that, by selection, can be enriched to become independent of the alteration in Hsp90. One might make the analogy that the capacitor model could serve as a form of assisted evolution for morphological traits whereas the rheostat model could provide assisted evolution for QTLs.

"Adaptive," or "stationary phase," mutation in bacteria is a stress response that promotes genomewide hypermutation (Rosenberg 2001). This can be viewed as a population-based, specialized form of evolution, which at first appeared to violate the principle that mutations occur independently of their phenotypic effects; in the end, adaptive mutation can be explained by undirected, stress-induced mutations followed by selection. Adaptive amplification is a somewhat similar response in bacteria, involving gene amplification rather than point mutation (Hastings et al. 2000). The rheostat hypothesis is particularly analogous to adaptive amplification, in that both imply that variability in the level of gene expression allows the organism to achieve adaptation to a changing environment.

Many of these forms of assisted evolution involve selective advantage at the level of the group. The rheostat hypothesis suggests a specialized form of evolution that involves the action of selection on individuals in a

specific environment, resulting in selective advantage to the group. The rheostat model implies a number of nontraditional perspectives: (1) an assisted and reversible component of evolution; (2) both genetic and epigenetic variants contributing to an integrated mechanism; (3) the possibility that the majority of variants are not intrinsically deleterious but are each potentially advantageous, depending on the environment; (4) the ability to protect a silent allele from selection, for many generations, but to reactivate and expand it in the population quickly; and (5) a component of epigenetic and non-Mendelian inheritance. We view the hypothesis as quite Darwinian in character, and we do not imply that mutations are directed.

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Electronic-Database Information

The URL for data in this article is as follows:

Mammalian Genetics Unit, Harwell UK, http://www.mgu.har.mrc.ac.uk/imprinting/imprinting.html

References

Balter M (2000) Genetics: was Lamarck just a little bit right? Science 288:38

Barker D, Schafer M, White R (1984) Restriction sites containing CpG show a higher frequency of polymorphism in human DNA. Cell 36:131–138

Bartolomei MS, Tilghman SM (1997) Genomic imprinting in mammals. Annu Rev Genet 31:493–525

Bell AC, Felsenfeld G (2000) Methylation of a CTCF-dependent boundary controls imprinted expression of the Igf2 gene. Nature 405:482–485

Bird A (2001) Molecular biology: methylation talk between histones and DNA. Science 294:2113–2115

——— (2002) DNA methylation patterns and epigenetic memory. Genes Dev 16:6–21

Boerkoel CF, Inoue K, Reiter LT, Warner LE, Lupski JR (1999) Molecular mechanisms for CMT1A duplication and HNPP deletion. Ann N Y Acad Sci 883:22–35

Chaillet JR (1994) Genomic imprinting: lessons from mouse transgenes. Mutat Res 307:441–449

Chicurel M (2001*a*) Genetics: can organisms speed their own evolution? Science 292:1824–1827

——— (2001*b*) Genetics: why evolution might not favor increased genetic variability. Science 292:1826

Dover G (2000) Results may not fit well with current theories. Nature 408:17

Gould SJ, Lloyd EA (1999) Individuality and adaptation across levels of selection: how shall we name and generalize the unit of Darwinism? Proc Natl Acad Sci USA 96:11904–11909

Gray TA, Saitoh S, Nicholls RD (1999) An imprinted, mammalian bicistronic transcript encodes two independent proteins. Proc Natl Acad Sci USA 96:5616–5621

Grunstein M (1997) Histone acetylation in chromatin structure and transcription. Nature 389:349–352

Hammond SM, Caudy AA, Hannon GJ (2001) Post-transcriptional gene silencing by double-stranded RNA. Nat Rev Genet 2:110–119

Hark AT, Schoenherr CJ, Katz DJ, Ingram RS, Levorse JM, Tilghman SM (2000) CTCF mediates methylation-sensitive enhancer-blocking activity at the H19/Igf2 locus. Nature 405:486–489

Hastings PJ, Bull HJ, Klump JR, Rosenberg SM (2000) Adaptive amplification: an inducible chromosomal instability mechanism. Cell 103:723–731

Henikoff S, Matzke MA (1997) Exploring and explaining epigenetic effects. Trends Genet 13:293–295

Hurst LD (1997) Evolutionary theories of genomic imprinting. In: Reik W, Surani A (eds) Genomic imprinting. IRL Press, Oxford, pp 211–237

——— (1998) Peromysci, promiscuity and imprinting. Nat Genet 20:315–316

Hurst LD, McVean GT (1998) Do we understand the evolution of genomic imprinting? Curr Opin Genet Dev 8:701–708

Jenuwein T, Allis CD (2001) Translating the histone code. Science 293:1074–1080

Kondrashov AS, Crow JF (1991) Haploidy or diploidy: which is better? Nature 351:314–315

Lindquist S (2000) But yeast prion offers clues about evolution. Nature 408:17–18

Lloyd V (2000) Parental imprinting in *Drosophila*. Genetica 109:35–44

Lloyd VK, Sinclair DA, Grigliatti TA (1999) Genomic imprinting and position-effect variegation in *Drosophila melanogaster.* Genetics 151:1503–1516

Matzke M, Matzke AJ, Kooter JM (2001) RNA: guiding gene silencing. Science 293:1080–1083

Mayr E (1997) The objects of selection. Proc Natl Acad Sci USA 94:2091–2094

McGowan RA, Martin CC (1997) DNA methylation and genome imprinting in the zebrafish, *Danio rerio:* some evolutionary ramifications. Biochem Cell Biol 75:499–506

Moore T, Haig D (1991) Genomic imprinting in mammalian development: a parental tug-of-war. Trends Genet 7:45–49

Morgan HD, Sutherland HG, Martin DI, Whitelaw E (1999) Epigenetic inheritance at the agouti locus in the mouse. Nat Genet 23:314–318

Nielsen SJ, Schneider R, Bauer UM, Bannister AJ, Morrison A, O'Carroll D, Firestein R, Cleary M, Jenuwein T, Herrera RE, Kouzarides T (2001) Rb targets histone H3 methylation and HP1 to promoters. Nature 412:561–565

Pembrey M (1996) Imprinting and transgenerational modulation of gene expression: human growth as a model. Acta Genet Med Gemellol (Roma) 45:111–125

Rakyan VK, Preis J, Morgan HD, Whitelaw E (2001) The marks, mechanisms and memory of epigenetic states in mammals. Biochem J 356:1–10

Reik W, Dean W (2001) DNA methylation and mammalian epigenetics. Electrophoresis 22:2838–2843
Reik W, Dean W, Walter J (2001) Epigenetic reprogramming in mammalian development. Science 293:1089–1093
Reik W, Walter J (2001) Genomic imprinting: parental influence on the genome. Nat Rev Genet 2:21–32
Rosenberg SM (2001) Evolving responsively: adaptive mutation. Nat Rev Genet 2:504–515
Rutherford SL, Lindquist S (1998) Hsp90 as a capacitor for morphological evolution. Nature 396:336–342
Seidman JG, Seidman C (2002) Transcription factor haploinsufficiency: when half a loaf is not enough. J Clin Invest 109:451–455
Shibata H, Yoshino K, Muramatsu M, Plass C, Chapman VM, Hayashizaki Y (1995) The use of restriction landmark genomic scanning to scan the mouse genome for endogenous loci with imprinted patterns of methylation. Electrophoresis 16:210–217
Silva AJ, White R (1988) Inheritance of allelic blueprints for methylation patterns. Cell 54:145–152
Sleutels F, Zwart R, Barlow DP (2002) The non-coding air RNA is required for silencing autosomal imprinted genes. Nature 415:810–813
Sommer SS, Scaringe WA, Hill KA (2001) Human germline mutation in the factor IX gene. Mutat Res 487:1–17
Sutherland HG, Kearns M, Morgan HD, Headley AP, Morris C, Martin DI, Whitelaw E (2000) Reactivation of heritably silenced gene expression in mice. Mamm Genome 11:347–355
True HL, Lindquist SL (2000) A yeast prion provides a mechanism for genetic variation and phenotypic diversity. Nature 407:477–483
Varmuza S (1993) Gametic imprinting as a speciation mechanism in mammals. J Theor Biol 164:1–13
Wolffe AP (2000) Transcriptional control: imprinting insulation. Curr Biol 10:R463–R465
Wolffe AP, Matzke MA (1999) Epigenetics: regulation through repression. Science 286:481–486
Wolff GL, Kodell RL, Moore SR, Cooney CA (1998) Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. FASEB J 12:949–957
Xin Z, Allis CD, Wagstaff J (2001) Parent-specific complementary patterns of histone H3 lysine 9 and H3 lysine 4 methylation at the Prader-Willi syndrome imprinting center. Am J Hum Genet 69:1389–1394